REMARKS/ARGUMENTS

The Status of the Claims.

Claims 3 to 6, 8, 12 to 15, 17, 18, and 20 to 23 are pending with entry of this amendment. Claims 2, 7, 9 to 11, 16 and 19 being cancelled. Claims 1, 3 to 6, 8, 15, 17 and 23 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to independent claims 1, 15 and 23, support for the 95% identity aspect and G:C pair at positions corresponding to 10:28 can be found throughout the specification. For example, see specification at paragraphs 15, 20, 23, 72, 75, 76, and 124; the Examples; and in Figures 1 and 4.

Other amendments are made at the suggestion of the Office with regard to informalities, such as antecedent basis or possible confusion.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

35 U.S.C. §112, First Paragraph.

Claims 1 to 3, 5, 6, 8, 12 to 16, 18 and 20 to 23 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement and lack of adequate written description. To the extent the amended claims continue to be deemed inadequate, Applicants traverse.

Current claims are well described in the original specification. An applicant may show adequate written description by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between

function and structure, or some combination of such characteristics. See, e.g., MPEP 2163, and *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613. Written description is often found where one skilled in the art is able to determine whether the composition claimed is the same as or different from a composition prepared by another by comparison to the claims in light of the specification.

Here, the currently amended claims are easy for one of skill to interpret and, e.g., understand what compositions would covered. Further, the claims include a genus of modest scope reflecting the range of provided species. For example, Applicants believe the cited consensus O-tRNA sequence 67 ranges from about 92% to 97% identity (even without counting the selector anticodon) with the tested functional O-tRNAs described in the original specification. In addition, the claims are specifically directed to the taught G:C at 10:28 consensus structure for Gln O-tRNAs identified as correlated to functionality in the genus of O-tRNAs. Because the current claims include identified functional structures and are limited to a genus well within the range of identified species, Applicants respectfully request withdrawal of the rejections for allegedly inadequate written description.

Current claims are enabled without undue experimentation. To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. See *id.*

In *Wands*, the Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. Therefore, the narrow range of working examples were held to enable claims to a very

broad genus. For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. See, MPEP 2164.

In the rejection of prior claims, the Office objected to the aspect of glutamyl-O-tRNA derived from an Archaeal with at least 80% sequence identity to SEQ ID NO: 67. However, the current claims are now further limited to require 95% identity. As noted above, the cited consensus O-tRNA sequence 67 ranges from about 92% to 97% identity (not counting the selector anticodon) with the tested functional O-tRNAs described in the original specification. Embodiments reduced to practice reasonably bracket the parameter of the claims. Moreover, the required G:C at 10:28 of the O-tRNA further focuses the claims on functioning structures enabled by teachings of the specification. Because the concerns of the Office have been entirely addressed, Applicants request withdrawal of rejections associated with the deleted 80% identity limitation.

The original specification enables one of skill at the time to fully practice the claimed inventions without undue experimentation. The claims are typically directed to compositions with a glutamyl O-tRNA limited to structures related to proper function and to sequence identity well within the range of embodiments reduced to practice. The specification teaches generic and specific methods, and identifies structures related to desired functions, allowing one of skill to practice a desired embodiment within the range of the claims, at will. For example, general methods and extensive technical references are provided in the O-tRNA section at paragraphs 70 to 86, and at paragraphs 174 to 179; and the O-RS section at paragraphs 87 to 94, and at paragraphs 173 and 186. Starting at paragraph 75, the specification teaches how to prepare libraries of consensus sequence derivatives having, e.g., 90% or 95% identity to the starting tRNA sequence. In the Examples sections, structure/functional information is provided for rational design considerations (substantially narrowing the experimentation required for success), such as the rationale for selection of

Archaea glutamyl systems for expansion of unnatural amino acid incorporation systems (paragraph 171), identification of glutamyl systems as predisposed to flexibility as orthogonal systems (paragraphs 184 and 185), the identification of G:C 10:28 as useful in Archaea tRNA recognition and orthogonality (extensively discussed in the specification); the usefulness of an "A" 3' to the anticodon to improve suppression efficiency (paragraph 181), and a problem to avoid with regard to his tags (paragraph 186).

Quantity of Experimentation. The first factor identified by the *Wands* Court was "(1) the quantity of experimentation necessary" to practice the claimed invention. In its analysis, the Court first noted that the experimental process for making antibodies that bound the relevant antigen were set forth in the application. In essence, this process included an elaborate hybridoma fusion screening and manipulation procedure, followed by a binding screen to identify "high binders" followed by another screening procedure to identify what type of antibody had been generated (IgM being the desirable antibody type in *Wands*). The PTO argued that less than 3% of hybridomas that were created produced antibodies, and of these, only 20% produced IgM antibodies. The first four hybridoma fusion experiments performed by the *Wands* inventors were failures, with the next 6 being successful. The Court held that this was not evidence of unpredictability, particularly given that the technique at issue was in general use for antibody production. *Wands* at 1406.

The quantity of experimentation would be relatively low to practice the present inventions. With the claims directed essentially to embodiments reduced to practice, including working species ranging across the genus of the claims, and given generic and specific methods to identify desired alternates, the claims could be successfully practiced with little experimentation. It is notable that, without the benefit of hindsight, the present inventors were able to identify various tRNAs (including the consensus sequence and many with close identity) that functioned in the compositions of the invention. Starting at paragraph 186, initial efforts identified 4 functioning Archaea RSs that worked orthogonally, all of which charged the O-tRNA to some degree (two of which functioned with a high degree of efficiency). Experimentation required to practice desired embodiments of the invention is much lower here than is was in *Wands*.

The Amount of Guidance. As discussed above, general and specific guidance provided is extensive. Large sections of the specification are dedicated to general methods of preparing the specific O-tRNAs and O-RSs of the invention, including large lists of helpful technical references. Examples 1 and 2 provide specific experimental materials and methods along with rationales for selecting functional sequences. Table 2 provides the consensus sequence and a large list of Archaeal tRNAs along with notations on relative frequencies and common alternates for each residue. The guidance provided guarantees success in practicing the invention.

Working Examples. The specification provides multiple O-RSs and O-tRNAs ranging across the breadth of the claims. The specification also includes working methods shown capable of providing additional compositions of the claims.

The State of the Art, Skill in the Art, and the Nature of the Invention. The state of the art and relative skill in the art are much higher here than in *Wands*. *Wands* indicated that the state of the prior art was advanced, with "all of the methods required to practice the invention being known." This is precisely true for the present case as well. Every step used to produce the claimed cells is known and available, and described or referenced in the specification. The level of skill of practitioners in the field was considered "high" for the *Wands* decision. Obviously, the skill in biotechnology is much higher now than it was in 1988. The information that biotechnology practitioners are presumed to be aware of has had over 20 years to develop, and the pace of development during that period has been staggering. A typical postdoctoral researcher or principal investigator can, for example, sequence and provide a detailed analysis of an entire genome, or, e.g., hundreds of cloned RS or OtRNA, in a matter of weeks, whereas in 1988, a week could go by to get one simple sequencing reaction to work, due to the extensive manual manipulations that had to be performed. If the level of skill in the art was "high" at the time of *Wands* then it is now positively stratospheric. In any case, any moderately competent molecular biologist, given Applicants' disclosure can certainly perform each and every step required to make the claimed compositions.

Predictability of the Art. In *Wands*, the Patent Office had argued that the "low" observed 2.8% rate of success in screening for antibodies in the case was evidence of

unpredictability. However, the Court took a different view, noting that in several of the cases in which an entire overall antibody production screen was performed, at least one antibody was produced. In the present case, in the many working examples provided, orthogonal components were routinely produced by the production screens of the invention. At paragraph 186, multiple orthogonal components were readily identified in the first try "as expected".

Breadth of Claims. The present claims are not unduly broad, given the enablement described above. Applicants note that the independent claims are currently amended to focus essentially on embodiments reduced to practice and species within the range of those embodiments. For example, the claims are typically limited to compositions with an O-tRNA having sequence identity within the range of percent identity for described working embodiments. The t-RNAs are further limited to the identified structural aspect of a G:C pair at a position corresponding to 10:28 associated in the specification with enhanced function in the context of the claimed compositions. Such claims are much less broad than the generic monoclonal antibody claims in enabled *Wands* patent without structural/ functional teachings and based on working examples not coming close to the range of the genus.

With regard to the claim 23 aspect of a glutamyl-RS having at least 90% identity to the four identified Archaeal glutamyl-RSs, one of skill could engineer functioning RSs in the range of the claims. One of skill can understand how the highly characterized O-tRNA of the claim can interact with the RSs, e.g., at binding pockets and active sites, and thus avoid loss of function in most cases. Archaeal glutamyl RS structures and functions are well characterized in the art, including the points of interaction between RSs and tRNAs. For example, one of skill understands protein structures generally, understands RS structures generally, and has available RS crystal structures and sequences for Archaea and *E. coli*. Even at lower levels of skill, one with basic knowledge in general protein chemistry and genetics could identify functional conservative variations with a predictability beyond the *Wands* standard.

Scientific journals often express amazement at finding amino acid substitutions in an active site that change activity of a peptide. However, it is unusual to find

the relatively rare mutations that destroy functionality, particularly outside of known points of external interaction, such as active sites and binding pockets. One of skill knows that anyone can readily identify functional conservative substitutions that do not change activity of a peptide, and that is why these observations of little interest and are rarely, if ever published. Given the available structural and functional information available, the guidance of the specification and working examples provided, the Office should reasonably agree that some RS variants beyond the identified sequences must reasonably be considered enabled. For example, one of skill in the art of protein engineering, given the reference sequence and synthetase structural information in the specification and the public domain could surely succeed with minimal experimentation in logical directed conservative substitution of 1%, 2% 5%, 10% 15% or more of amino acids along the given sequence. Avoiding known and identified structural elements, one could easily substitute amino acids conducive to maintenance of scaffolding structures, such as α helices and β sheets, without disrupting secondary and tertiary conformations. Even if such substitutions influenced peptide activity, the result would often be a changed activity without total loss of function. Because one of skill could identify functional RSs with up to 10% of the amino acids conservatively substituted (e.g., on physical structures outside known tRNA interaction sites) without undue experimentation, the claim is enabled.

Because the claims have been amended to remove terms objected to as overly broad and lacking enablement, the rejections should be withdrawn. Because the current claims are far better enabled than those found enabled in *Wands*, Applicants request the claims be deemed enabled and allowable by the Office.

Allowable Claims.

Applicants appreciate the Examiner's indication that claims 4 and 17 are allowable.

Claim Objections.

Claim 4 was objected to for logical inability of a tRNA to be both comprise and be encoded by the same sequence. Applicants appreciate the careful reading of the Office and have amended claim 4 to further clarify the nature of the sequences.

Claims 17 and 22 were objected to for certain informalities. Applicants have amended the claims, as suggested in the Action.

Claims 3, 5, 6 and 8 were objected to for lacking particular antecedent basis regarding the "selector codon" recitation. Applicants appreciate the careful reading by the Examiner and have adjusted the claims according to the suggestions in the Action.

Because Applicants have addressed the claim objections of record, they respectfully request withdrawal of the objections.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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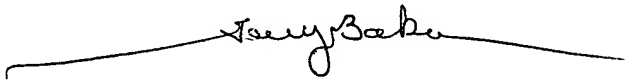
Respectfully submitted,



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Attachments:

1) A transmittal sheet; and,
2) A receipt indication postcard.